# EXHIBIT 15

Acta Neurol Scand 1998: 97: 164–170
Printed in UK – all rights reserved


ACTA NEUROLOGICA SCANDINAVICA
ISSN 0001-6314

# Pregnancy and epilepsy: a retrospective study of 151 pregnancies

Sabers A, a'Rogvi-Hansen B, Dam M, Fischer-Rasmussen W, Gram L, Hansen M, Møller A, Winkel H. Pregnancy and epilepsy: a retrospective study of 151 pregnancies.
Acta Neurol Scand 1998: 97: 164–170. © Munksgaard 1998.

*Objective* – We studied the course of pregnancy in women with epilepsy to identify possible risk factors which might complicate the epilepsies and pregnancy outcomes. *Material and methods* – Data were collected retrospectively from the records of 151 pregnancies in 124 women with epilepsy from 1978–1992. Epilepsy variables were compared with that of non-pregnant women with epilepsy mached for age. Obstetric and neonatal variables were compared with those of all deliveries in the same unit from 1979–1992 ($n$=38,983). *Results* – Pregnancy among patients with epilepsy was more likely to occur in women with relatively mild epilepsy. In 12% of the pregnancies, the women were untreated while 71% were on monotherapy. Twenty-one percent had increased seizure frequency during the pregnancy. Perinatal deaths among newborns of epileptic mothers (1.3%) was more frequent but not significantly increased compared to the background population of 0.5% (95% CI 0.2–4.7). A total of 5.3% had congenital malformations compared to 1.5% in the controls (95% CI 2.3–10.3). No neural tube defects were observed. Maternal treatment with phenytoin was significantly related to the occurrence of congenital malformations, $P$=0.04. *Conclusions* – Most women with epilepsy have an uncomplicated pregnancy and normal healthy offsprings. Maternal treatment with phenytoin might be associated with congenital malformations. No other risk factors could be identified.

**A. Sabers[1], B. a'Rogvi-Hansen[1], M. Dam[1], W. Fischer-Rasmussen[2], L. Gram[1], M. Hansen[2], A. Møller[3], H. Winkel[1]**

[1]University Clinic of Neurology, [2]Department of Obstetrics and Gynecology, Hvidovre Hospital, University of Copenhagen, DK-2650 Hvidovre, Denmark, and [3]Neuro-Search A/S Smedeland 26, DK-2600 Glostrup, Denmark

Key words: epilepsy; pregnancy; anticonvulsants; perinatal mortality; congenital malformations

A. Sabers, Dianalund Epilepsy Hospital, Kolonivej 1, DK-4293, Denmark

Accepted for publication October 16, 1997

Women with epilepsy who are pregnant or want to become pregnant form a substantial number in most epilepsy clinics.

Previous studies have demonstrated that women with epilepsy are at risk for a variety of complications during pregnancy. Twenty-five to 30% of the women will experience seizure exacerbation (1, 2). A higher number of neonatal deaths are frequently reported (3–5) and infants of women with epilepsy have an increased risk of being born with malformations compared to the rest of the population (6–8).

The antiepileptic drugs taken before and during pregnancy, the maternal seizure frequency and seizure types are all variables that might influence outcome.

Optimizing pregnancy outcome and counselling of the patients with epilepsy, will still require an increased knowledge of specific risk factors.

The aim of this retrospective study was to describe the course of pregnancies in women with epilepsy, and identify possible specific risk factors which may have complicated the epilepsies and/or pregnancy outcomes. The present paper focused on the neurological complications and fetal outcome, while obstetrical details will be given in a separate report.

## Material and methods

The study included all women with epilepsy who had given birth at the Department of Obstetrics and Gynecology, Hvidovre University Hospital, during the years 1978–1992. The population was drawn from the local geographic region and reflected a significant proportion of patients with epilepsy in the city of Copenhagen.

Data were collected retrospectively and comprised 153 deliveries in 125 women. Twin births (1 case) were excluded due to the general high risk of obstetric complications in these patients, leaving 151 deliveries in 124 women for analyses.

The study population was derived from the hospital computerized database registrations of

discharge diagnoses. The hospital has a one in whole case record system for each patient, which guarantees identification of the epilepsy diagnosis for those associated to the neurological department (85%). In these cases the epilepsy classification was determined by an epileptologist (M.D. or L.G.). The ascertainment of the epilepsy diagnosis of the pregnant women who were not associated to the neurological department depended on self-reported obstetrical request forms, and the epilepsy syndrome was in most cases regarded as unclassified. Seizure types were classified according to The International League Against Epilepsy (ILAE) classification (9).

The mean age of the women at time of the pregnancy was 26.5 years (17–42 years). Twenty-three women were studied during 2 pregnancies and 2 during 3 pregnancies.

The duration of maternal epilepsy was 128 months (0–408 months).

Most patients (93%) made a routine prenatal visit to a consultant obstetrician (W.F.R.) approximately every month (average 5.5 visits). Neurological care for the subjects was carried out at the Department of Neurology by, or under supervision of, an epileptologist (M.D. or L.G.).

Changed seizure frequency during the pregnancy reflected the average sum of total seizures per 3 months prior to pregnancy, compared to the average sum of total seizures per trimester during the pregnancy. The seizure frequency was regarded as increased, if women with complete control preconceptionally had a single relapse during the pregnancy. The accuracy of the seizure counts before and during the pregnancy depended on the patient's individual exactness. All women associated to the neurological department were expected to use a seizure diary, and the number of seizures were noted at each visit.

Plasma levels of antiepileptic drugs (AEDs) were in general adjusted to keep steady-state plasma levels within the prepregnant range of the individual patient. In case of seizure deterioration, dosages were adjusted and in a few cases the type of AEDs was changed.

The pregnant women were compared to non-pregnant women with epilepsy matched for age ($n$=232), who were monitored at the epilepsy clinic of the Department of Neurology in 1994.

Infants were examined by a pediatrician on the day of birth and on the 5th day after birth.

Obstetric and neonatal variables were compared with those of all deliveries in the same unit from 1979–1992 ($n$=38,983).

Amniocentesis is centralized in another hospital in Copenhagen. It was not possible to identify cases of late induced abortions in our study population, due to an abnormal result of an amniotic fluid analysis, e.g. increased alpha-1-fetoprotein.

Statistics: For statistical analysis the chi-square and Fisher's exact tests for 2×2 tables were used. Differences were considered of statistical significance for $P$-values<0.05.

## Results

The pregnant women with epilepsy were significantly more likely to have primary generalized seizures compared to the group of age matched non-pregnant women with epilepsy (Table 1). The number of patients with unclassified epilepsy syndromes were significantly more frequent in the pregnant group, which reflects the patients who were unknown by the epilepsy clinic prior to delivery. More patients in the pregnant group were managed without AEDs (12%), or were prescribed single drug therapy (71%) compared to the non-pregnant patients (4% and 60%, respectively).

The pregnant women with epilepsy were mainly treated with carbamazepine (CBZ) (40%), sodium-valproate (VPA) (24%), and phenytoin (PTH) (14%). Other drugs: ethosuximide (ETX), clonazepam (CNP), clobazam (CLB), phenobarbital (PB), oxcarbazepine (OXC), primidone (PRM), and vigabatrin (VGT) were all prescribed in less than 10% of the pregnancies.

### Frequency of seizures during pregnancy

Three women had their first seizure during the pregnancy. In 96 cases (64%), the women had been

Table 1. Seizures and syndromes in pregnant ($n$=151) and non-pregnant patients with epilepsy ($n$=232) matched for age

| | Pregnant patients | Non-pregnant patients with epilepsy |
|---|---|---|
| Seizure type | | |
| Absences | 22 (15%)# | 24 (10%) |
| Atypical absences | 1 (0.5%)# | 14 (6%) |
| Myoclonic | 15 (10%) | 29 (12%) |
| Complex partial | 53 (35%) | 98 (42%) |
| Simple partial | 11 (7%)» | 64 (28%) |
| Tonic/clonic | 84 (55%)* | 79 (34%) |
| Sec. generalization | 34 (23%)# | 122 (53%) |
| Atonic | 0 | 5 (2%) |
| Unclassified | 2 (1.5%) | 10 (4%) |
| Epileptic syndromes | | |
| Generalized idiopathic | 68 (45%) | 87 (38%) |
| Generalized symptomatic | 6 (4%) | 8 (3%) |
| Partial idiopathic | 2 (1.5%) | 12 (5%) |
| Partial symptomatic | 55 (36%)# | 125 (54%) |
| Unclassified | 20 (13.5%)* | 0 |

Difference of statistical significance compared with the non-pregnant group. #$P$<0.05, »$P$<0.005, * $P$<0.0005.

seizure-free 3 months prior to pregnancy. Thirty-seven pregnant women (24%) had 2 seizures or less per month, and 12 (8%) had more than 2 seizures per month before pregnancy. In 6 cases (4%) pre-pregnant data were unknown.

Seventy-nine of the 96 pregnancies of which the women were seizure-free prior to pregnancy, continued without seizure relapse throughout the pregnancy. Eleven patients were untreated throughout the pregnancy, and 25 had the AED dosage adjusted during the pregnancy.

The changes in total seizure frequency during pregnancy compared to the last 3 months prior to pregnancy are shown in Fig. 1. In 98 pregnancies (66%) seizure frequency was unchanged, including the 79 patients (52%) who were seizure-free before pregnancy and remained seizure-free throughout pregnancy. Seizure frequency was increased in 32 (21%) and decreased in 11 (7%). In 10 patients (6%), data about seizure frequency were insufficient.

Increased seizure frequency was not related to the seizure types or the epileptic syndromes. In 27 (84%) of patients with increased seizure frequency the women had been seizure-free or had 2 or less seizure per month prior to the pregnancy. Eight patients had a single relapse during the pregnancy. If these patients were excluded from the group with increased seizure frequency, the incidence of seizure deterioration was 16%. The frequency of seizure deterioration in patients who previously were seizure-free or had 2 or less seizures per month ($n$=139), was 19.4% and in patients with more than 2 seizures per month ($n$=12) was 42% ($P$=0.07).

Two patients who had increased seizure frequency did not receive any AED, and had been seizure-free prior to pregnancy. In the other patients the plasma levels of AED were in general low within the optimal range. Three of the patients with increased seizure frequency were regarded as non-compliant. In 5 cases compliance was unknown and in the remainder (75%), compliance was assessed as adequate.

In general the seizure frequency increased equally in the 3 trimesters. In 5 cases the seizure frequency was increased throughout the pregnancy.

In patients studied during more than 1 pregnancy, 3 patients experienced increased seizure frequency in 2 pregnancies and in 9 patients the seizure frequency was increased in only 1 pregnancy.

There was no status epilepticus during pregnancy.

### Seizures during delivery and puerperium

Four women (2.6%) experienced seizures during delivery. Two had a complex partial seizure and 2 had a generalized tonic–clonic seizure. In 2 of them the seizure frequency had been increased during the pregnancy, and the other 2 women had been seizure-free throughout pregnancy. All these women received antiepileptic medication, and compliance was regarded as adequate.

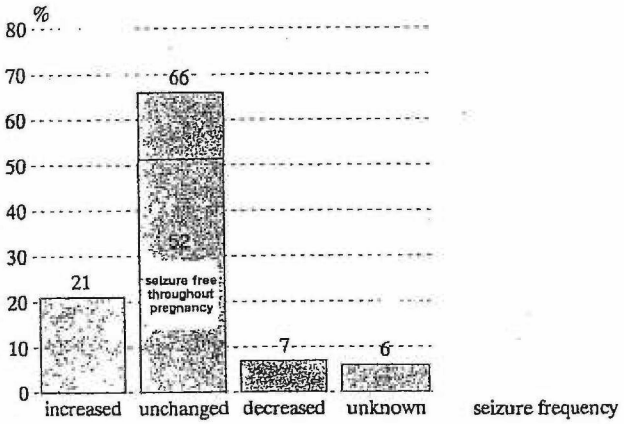


*Fig. 1.* Changes of total seizure frequency during pregnancy compared to the last 3 months prior to pregnancy ($n$=151).

Eight patients had seizures (5%) during the puerperium, 5 of them had generalized tonic–clonic seizures and 3 partial seizures. Two patients had been seizure-free without AED throughout the pregnancy. The others were all treated with CBZ. Plasma levels at delivery ranged from 18–27 µmol/l.

### Neonatal outcome

Infants of women with epilepsy were comparable to the background population with respect to sex distribution, birth weight and gestational age at delivery (Table 2). The infant head circumference at birth averaged 34.7 cm in newborns of women with epilepsy (boys 35.0 cm, girls 34.3 cm), which

Table 2. Neonatal outcome in 151 pregnancies of women with epilepsy compared to a background cohort of 38,983 women

| | Women with epilepsy | | | Controls | |
|---|---|---|---|---|---|
| | *n* | % | 95% CI | *n* | % |
| Sex distribution: | | | | | |
| girls | 72 | 48 | (40.5–57.0) | 18,751 | 48 |
| boys | 79 | 52 | (43.7–60.1) | 20,460 | 52 |
| Birth weight: | | | | | |
| <2500 g | 7 | 5 | (1.9–9.4) | 2,699 | 7 |
| 2500–4500 g | 137 | 90 | | 34,843 | 89 |
| >4500 g | 7 | 5 | (1.9–9.4) | 1,458 | 4 |
| Pre-term births | 7 | 5 | (1.9–9.4) | 2,699 | 7 |
| Referral to intensive neonatal care unit | 30 | 20 | (13.9–27.3) | 2,700 | 7 |
| Perinatal deaths | 2 | 1.3 | (0.2–4.7) | 181 | 0.5 |
| Fetal malformations | 8 | 5.3 | (2.3–10.3) | 585 | 1.5 |

was comparable to the average head circumference of 34.9 cm (boys 35.2 cm, girls 34.6 cm), in randomly chosen infants born in Copenhagen from 1985–1988 (10).

Newborns of mothers with epilepsy were 3 times more likely to be monitored at the intensive neonatal care unit ($n$=30). Thirteen of these (42%) were asphyxic at delivery.

The number of perinatal deaths was 2 (1.3%, 95% CI 0.2–4.7), compared to 0.5% in the background population. The 2 dead infants were born in 1982 and 1991, respectively. One infant born mature (4050 grams) was asphyxiated due to aspiration of meconium and died 26 h after delivery following sepsis and disseminated intravascular coagulation. The other infant was born premature (1145 grams) at 28 weeks of gestation and died because of severe asphyxia. Neither infants were malformed, and the mothers had not previously had malformed or perinatal dead children.

Amniocentesis was performed in 34% of the pregnancies, which is 4 times more frequent than in controls. Outcomes of the amniocentesis were not available as this procedure is centralized in another hospital in Copenhagen.

### Fetal malformations

Among the 151 pregnancies, there were 8 children (5.3%) with congenital malformations, one each with ventricular septum defect, double sided cleft lip and palate, bilateral metatarsus varus (sufficiently treated with bandages), polydactyli, luxatio coxae, and 3 cases of hypospadia. There were no neural tube defects. The children with malformations were borne by different women, mean age 26 years (21–38 years). All the women were taking AEDs (Table 3). One woman was treated with polytherapy (CNP 3 mg/day, PB 100 mg/day, and PTH 375–450 mg/day). The other women were on monotherapy; PTH $n$=2 (dose range 200–300 mg/day), CBZ $n$=2 (dose range 600–800 mg/day), VPA $n$=3 (dose range 1000–1500 mg/day). One woman was given VPA once a day until the 11th week of gestation, where the dosage was divided and another patient was treated once a day throughout pregnancy. The dose regime was unknown in 1 woman treated with VPA.

The risk of malformation was significantly related to treatment with PTH ($P$=0.040) but only when the patient on 3-drug therapy was included in the analysis (Table 4). The infants with congenital malformations were born between 1979 and 1992.

## Discussion

The present findings indicate that pregnancy among patients with epilepsy are more likely to occur in women with relatively mild epilepsy. Only a minority of the pregnant women were on polytherapy, and symptomatic epilepsy was significantly less frequent in the pregnant compared to the non-pregnant women with epilepsy. The non-pregnant controls were not examined at the same time (1994) as the pregnant women (1978–1992) which might influence the results.

Most patients were well controlled prior to pregnancy, as 88% were seizure-free or had less than 2 seizures per month. Twenty-one percent of the patients had increased seizure frequency during pregnancy. The risk of seizure deterioration tended to be related to a seizure frequency higher than 2 per month, whereas no other risk factors were found. Most patients were frequently monitored during pregnancy and plasma concentration levels of the AEDs were in general adjusted within optimal ranges.

The frequency of seizure deterioration during pregnancy reported in the literature has presented a variable picture. In a review of 2165 pregnancies based on 27 studies during 1884–1980, the incidence of increased seizure frequency ranged from 4–75% (1). The studies are difficult to compare, as

Table 3. Antiepileptic medication in mothers given birth to children with congenital malformations

| Fetal malformation | $n$ | Maternal AED treatment |
|---|---|---|
| Ventricular septum defect | 1 | VPA 1000–1500 mg/day (plasma-level: 302–318 µmol/l) |
| Bilateral cleft lip and palate | 1 | PTH 200 mg/day* |
| Bilateral metatarsus varus | 1 | CBZ 800 mg/day (plasma-level: 28 µmol/l) |
| Polydactyli | 1 | PTH 375–450 mg/day (plasma-level: 32–30 µmol/l)<br>PB 100 mg/day (plasma-level: 58–67 µmol/l)<br>CNP 3 mg/day* |
| Luxatio coxae | 1 | VPA 1200 mg/day* |
| Hypospadia | 3 | 1: CBZ 600 mg/day*<br>2: PTH 300 mg/day*<br>3: VPA 1200 mg/day (plasma-level: 289–358 µmol/l) |

* Plasma level not available.

Table 4. Maternal drug therapy and congenital malformation

| Drugs | Total number of patients treated with the drug | Fetal malformations of patients treated with the drug | *P*-value | ODDS ratio |
|---|---|---|---|---|
| CBZ | 60 | 2 | 0.36 | 0.48 |
| PTH | 20 | 3 | 0.040* | 4.38 |
| CNP | 13 | 1 | 0.67 | 1.54 |
| VPA | 41 | 3 | 0.52 | 1.63 |
| PB | 10 | 1 | 0.45 | 2.10 |

* Statistically significant.

discussed later, but it is interesting that pooled data indicated that increased seizure frequency during pregnancy occurred with an average of 24% in the 2165 pregnancies (1), which is consistent with our results and the results of Lander and Eadie (2), who demonstrated seizure deterioration in 25.4% of 122 pregnancies. In 4 prospective studies, seizures increased in 8%, 32%, 41% and 46%, respectively (11–14), whereas other studies conclude that pregnancy has a limited effect on seizure frequency (5, 15).

Evaluating seizure deterioration during pregnancy is difficult as seizure frequency in epilepsy is characterized by fluctuations in itself. In addition, the great range of reported incidences of increased seizure frequency may at least partly be influenced by the development in medical treatment and monitoring, and on what is graded as an increase. Most studies do not specify the calculation method. Bardy (12) considered the seizure frequency increased if the number of seizures was 200% or more of the pre-pregnant number. Canger et al. (13) considered mainly major seizures. In the present study the seizure frequency was regarded as increased if there was only 1 single relapse during the pregnancy.

A variety of theories have been suggested to explain the deterioration. Several studies have demonstrated that the pharmacokinetics of AEDs are altered during pregnancy with a decline of plasma levels as pregnancy progresses (15–19). Yerby et al. (20) reported a significant decrease of plasma concentrations of AEDs, but the free level of CBZ, PTH and VPA remained stable. Only the plasma level of free PB decreased. In the study by Lander and Eadie (2) one quarter of the women had increased seizure frequency, although the patients were closely monitored and decrease in plasma concentration of AEDs was adjusted. One third of these patients were untreated at outset of pregnancy. Among the patients receiving AED, increased seizure frequency was more than double in patients who were not fully controlled, compared to patients with complete seizure control prior to pregnancy. Other studies found increased seizure frequency associated with non-compliance or inadequate dosage adjustment (11), severity and duration of epilepsy (14). Bardy (12) and Canger et al. (13) were not able to identify any specific factors predicting increased seizure frequency.

In our study as in most other studies, the seizure frequency was unchanged during the pregnancy in the majority of the patients including those who were seizure-free before and throughout pregnancy. A previous review of older and more recent reports, demonstrated a trend of a gradually increasing number of pregnancies being completed without changes of seizure frequency (21). The number of patients with improved seizure control declined simultaneously. This probably reflects the fact that most patients today are very well controlled as in our study, where 64% of the women had been seizure-free at least 3 months prior to conception.

Seizures occurred during delivery or puerperium in 8% in the present study. This is lower than reported by Akhtar and Millac (5) and Schmidt (11), who claimed that the epileptic mothers are especially vulnerable during the puerperium probably due to sleep deprivation and discontinuation of medication. Apart from the 2 untreated patients in our study, no specific risk factors could be predicted. None of the patients had seizures both during delivery and puerperium.

The perinatal mortality in this study was higher, but not significantly different from that of the background population. The figure of 1.3% in our study is remarkably low compared to other authors, e.g. Knight and Rhind (3), Källen (4), and Akhtar and Millac (5), reporting 4.7%, 2.7%, and 4.2%, respectively. The low perinatal mortality may be the result of better perinatal care in general. The perinatal mortality decreased from 4.7% during 1977–1981 to 2.1% during 1987–1991. However, the perinatal mortality was 2 to 3 times that of controls in both periods (22).

The incidence of preterm births, birth-weight and neonatal head circumference of infants of mothers with epilepsy did not differ from those of the background population. Similar results were found by Hunter and Allen (23). However, an increased number of intrauterine growth retardation amongst infants of women with epilepsy has been observed in other studies (22, 24–26).

The infants of epileptic mothers were 3 times more likely to be observed at the intensive neonatal care unit compared to the background population. This reflects both an increase in neonatal complications and, probably, a result of increased attention to the infant of an epileptic mother.

The prevalence of congenital malformations (5.3%) was approximately 3 times greater than in the background population. All mothers of infants with malformations were exposed to AED before and during pregnancy, 7 on monotherapy and 1 on polytherapy. Excluding the 12 untreated patients in this study gives a risk of malformation in exposed women of 5.8%. This is somewhat lower than previously reported; Annegers and Hauser (27), found 10.7%, Lindhout et al. (28) 9.9%, Kaneko et al. (29) 13.5%, Hunter and Allen (23) 10%, Sharki and Abdulwahab (30) 14.4%, Battino et al. (31) 9.1%, Dravet et al. (32) 7%, Lindhout et al. (33) 7.6%, Kaneko et al. (34) 6.2%. A reason for the discrepancy could be differences in the time of follow-up, or reflect changes in AED treatment. Annegers and Hauser (27) found congenital malformations in 4.5% at the time of birth in infants exposed to AEDs *in utero*, whereas the number of observed malformations were more than doubled (10.7%) when the children were examined at 20 years of age. In the study by Kaneko et al. (29) the children were followed up to the time of important developmental stages. Lindhout et al. (33) compared the prevalence of congenital malformations during 1972–1979 and 1980–1985 where the number of malformations decreased from 10% to 7.6%, respectively. During the 2nd period the prescribing of PB, PTH and PRM had dropped markedly, whereas monotherapy with VPA or CBZ had increased. Similar results were found by Kaneko et al. (34), who compared the outcome in 2 prospective studies from 1978–1984 and 1985–1989. The occurrence of congenital malformations was reduced from 13.5% to 6.2% from the 1st to the 2nd period. A significantly increased number of women received monotherapy, during the 2nd period (63% compared to 16%). In the present study the majority of women were on monotherapy, and the plasma levels of AED were relatively low. Others have demonstrated congenital malformations being related to polytherapy (4, 30, 35) and maternal plasma levels of AED (36).

In our study the occurrence of malformations was significantly related to treatment with PTH, but only when the patient on 3-drug therapy was included in the analysis. Other risk factors could not be identified, but some drugs, especially the newer OXC and VGT, were only given to a small number of patients.

No cases of neural tube defects could be traced. This could be due to our sample size. The expected rate of neural tube defects in offsprings of women treated with VPA is 1–2% (37) and with CBZ 0.5–1% (38). Alternatively, some women might have had an induced abortion in another hospital due to an abnormal result of the amniotic fluid analysis. However, we were not able to reveal any evidence to support this.

In conclusion, the present study demonstrated that some women with epilepsy, approximately 20%, had a risk of increased seizure frequency during pregnancy compared to the nearest 3-month period prior to pregnancy. They could not be identified by their former seizure frequency, seizure type, or epileptic syndrome. A 3-doubled prevalence of congenital malformations in infants of women with epilepsy compared to the background population was recognized. The majority of malformations were not severe. Congenital malformations were found to be associated with maternal treatment with PTH. The study included few women treated with newer AEDs. Several new AEDs have been introduced in the last few years, e.g. OXC, VGT, lamotrigine, gabapentin, tiagabine and topiramate. As many fertile women are and will be exposed to these newer drugs, prospective studies of larger cohorts are required to assess possible teratogenic effects.

It is recommended that optimal seizure control is achieved prior to conception and that monotherapy with the lowest effective dosage be employed. With qualified prenatal medical and obstetric care, the great majority of women with epilepsy can be assured of an uncomplicated pregnancy and of normal healthy offsprings.

## References

1. Schmidt D. The effect of pregnancy on the natural history of epilepsy: Review of the literature. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 3–14.
2. Lander CM, Eadie MJ. Plasma antiepileptic drug concentrations during pregnancy. Epilepsia 1991: 32(2): 257–66.
3. Knight AH, Rhind EG. Epilepsy and pregnancy: A study of 153 pregnancies in 59 patients. Epilepsia 1975: 16: 99–110.
4. Källen B. A register study of maternal epilepsy and delivery outcome with special reference to drug use. Acta Neurol Scand 1986: 73: 253–9.
5. Akhtar N, Millac P. Epilepsy and pregnancy: A study of 188 pregnancies in 92 patients. Br J Clin Pract 1987: 41(8): 862–4.
6. Delgado-Escueta AV, Janz D. Consensus guidelines: Preconception counseling, management, and care of the pregnant woman with epilepsy. Neurology 1992: 42(Suppl. 5): 149–60.
7. Lindhout D, Omtzigt GC. Teratogenic effects of antiepileptic drugs: implications for the management of epilepsy in women of childbearing age. Epilepsia 1994: 35(Suppl. 4): 19–28.
8. Steegers-Theunissen RPM, Renier WO, Borm GF et al. Factors influencing the risk of abnormal pregnancy outcome in epileptic women: A multi-center prospective study. Epilepsy Res 1994: 18: 261–9.
9. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981: 22: 489–501.

10. Michaelsen KF, Petersen S, Greisen G, Thomsen BL. Weight, length, head circumference, and growth velocity in a longitudinal study of Danish infants. Dan Med Bull 1994: 41: 577–85.
11. Schmidt D. The effect of pregnancy on the course of epilepsy: A prospective study. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 39–49.
12. Bardy AH. Seizure frequency in epileptic women during pregnancy and puerperium: Results of the prospective Helsinki study. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 27–31.
13. Canger R, Avanzini G, Battino D, Bossi L, Franceschetti S, Spina S. Modifications of seizure frequency in pregnant patients with epilepsy: A prospective study. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 33–8.
14. Remillard G, Dansky L, Andermann E, Andermann F. Seizure frequency during pregnancy and the puerperium. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 15–26.
15. Luef G, Marosi M, Pohl P, Bauer G. Monitoring of antiepileptic drugs during pregnancy. Nervenarzt 1991: 62(12): 750–3.
16. Mygind KI, Dam M, Christiansen J. Phenytoin and phenobarbitone plasma clearance during pregnancy. Acta Neurol Scand 1976: 54: 160–6.
17. Dam M, Christiansen J, Munck O, Mygind KI. Antiepileptic drugs: Metabolism in pregnancy. Clin Pharmacokinet 1979: 4: 53–62.
18. Bardy AH, Hiilesmaa VK, Teramo KAW. Serum phenytoin during pregnancy, labor and puerperium. Acta Neurol Scand 1987: 75: 374–5.
19. Yerby MS, Friel PN, McCormick K et al. Pharmacokinetics of anticonvulsants in pregnancy: alterations in plasma protein binding. Epilepsy Res 1990: 5: 223–8.
20. Yerby MS, Friel PN, McCormick K. Antiepileptic drug disposition during pregnancy. Neurology 1992: 42(Suppl. 5): 12–6.
21. Sabers A, Dam M. Pregnancy, delivery, and puerperium. In: Dam M, Gram L, eds. Comprehensive Epileptology. New York: Raven Press, 1990: 299–307.
22. Martin PJ, Millac PAH. Pregnancy, epilepsy, management and outcome: a 10 years' perspective. Seizure 1993: 2: 277–80.
23. Hunter RW, Allen EM. The course and outcome of pregnancy in women with epilepsy – a 6-year prospective study. J Obstet Gynaecol 1990: 10: 483–91.
24. Yerby M, Koepsell T, Daling J. Pregnancy complications and outcomes in a cohort of women with epilepsy. Epilepsia 1985: 26(6): 631–5.
25. Mastroiacovo P, Bertollini R, Licata D. Fetal growth in the offspring of epileptic women: results of an Italian multicentre cohort study. Acta Neurol Scand 1988: 78: 110–4.
26. Gailey E, Granström ML. A transient retardation of early post-natal growth in drug exposed children of epileptic mothers. Epilepsy Res 1989: 4: 147–55.
27. Annegers JF, Hauser WA. The frequency of congenital malformations in relatives of patients with epilepsy. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 267–73.
28. Lindhout D, Meinardi H, Barth PG. Hazards of fetal exposure to drug combinations. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 275–81.
29. Kaneko S, Otani K, Fukushima Y et al. Teratogenicity of antiepileptic drugs: analysis of possible risk factors. Epilepsia 1988: 29(4): 459–67.
30. Sharki RA, Abdulwahab B. Congenital malformations before and after the onset of maternal epilepsy. Acta Neurol Scand 1991: 84: 153–6.
31. Battino D, Binelli S, Caccamo ML et al. Malformations in offspring of 305 epileptic women: a prospective study. Acta Neurol Scand 1992: 85: 204–7.
32. Dravet C, Julian C, Legras C et al. Epilepsy, antiepileptic drugs, and malformations in children of women with epilepsy. Neurology 1992: 42(Suppl. 5): 75–82.
33. Lindhout D, Meinardi H, Meijer JWA, Nau H. Antiepileptic drugs and teratogenesis in two consecutive cohorts. Neurology 1992: 42(Suppl. 5): 94–110.
34. Kaneko S, Otani K, Kondo T et al. Malformation in infants of mothers with epilepsy receiving antiepileptic drugs. Neurology 1992: 42(Suppl. 5): 68–74.
35. Rating D, Jäger-Roman E, Koch S, Göpfert-Geyer I, Helge H. Minor malformations in the offspring of epileptic parents. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 283–8.
36. Dansky L, Andermann E, Andermann F, Sherwin AL, Kinch RA. Maternal epilepsy and congenital malformations: correlation with maternal plasma anticonvulsant levels during pregnancy. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 251–8.
37. Omtzigt JGC, Los FJ, Grobbee DE et al. The risk of spina bifida aperta after first trimester valproate exposure in a prenatal cohort. Neurology 1992: 42(Suppl. 5): 119–25.
38. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. N Engl J Med 1991: 324: 674–7.